*Chemistry of Heterocyclic Compounds, Vol. 32, No. 9, 1996*

# STEREOSELECTIVITY IN THE REDUCTION OF CHIRAL INDOLES TO INDOLINES

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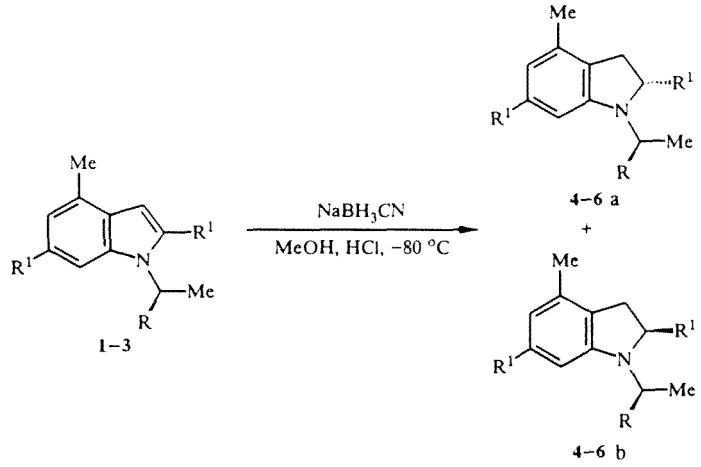
*The reduction of 2-alkylindoles containing a chiral substituent at the nitrogen atom by sodium cyanoborohydride in an acidic medium at −80°C is accompanied by the formation of indolines with S-configuration of the new chiral site at $C_{(2)}$. An AM1 quantum chemical calculation showed that the major diastereomer has greater thermodynamic stability. However, the high diastereoselectivity of this reduction may be attributed only to the relative stability of the different conformations of the intermediate indoleninium cations leading to different diastereomers.*

We have recently developed a new method for the synthesis of 2-alkylindoles containing a chiral substituent at the nitrogen atom and demonstrated the feasibility of the stereoselective reduction of the indoles obtained to give indolines [1]. In the present work, we studied the effect of steric factors on the diastereoselectivity of the reduction of such indoles. Indoles **1-3** were taken as models for studying the effect of substituents on the stereoselectivity of the reduction:




1, 4 R = Ph, $R^1$ = Me; 2, 5 R = Ph, $R^1$ = Et; 3, 6 R = $CH_2Ph$, $R^1$ = Me

In selecting the models, we assumed that the environment of both the chiral and prochiral sites affects the diastereoselectivity of the reduction of such indoles. Indoles **1-3** were obtained by the transformation of 3-nitropyridinium salts by the action of the corresponding acetonimines analogously to our previous procedure [1]. In order to minimize consumption of the optically active primary amines, the reaction with the 3-nitropyridinium salt was carried out in the presence of the hydrochloride of the corresponding amine in order to suppress transamination reactions leading to 1-methylindoles [1]. An enantiomerically pure substrate is not required for evaluating asymmetric induction since modern analytical methods such as NMR spectroscopy permit us to determine the ratio of the diastereomeric racemates [*RR*] + [*SS*]/[*RS*] + [*SR*] [2]. Hence,

M. V. Lomonosov Moscow State University, 119899 Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1199-1208, September, 1996. Original article submitted August 30, 1996.

0009-3122/96/3209-1027$15.00  

TABLE 1. Reduction Conditions and Ratio of Diastereomers Obtained in the Reduction of Indoles **1-3**

| Indole | Indole/$NaBH_3CN$ ratio | Reduction time, h | Diastereomer ratio | Yield, % |
|---|---|---|---|---|
| (*S*)-**1** | 1 : 2 | 1 | 9 : 1 | 88 |
| (*S*)-**2** | 1 : 6 | 3,5 | 99 : 1 | 92 |
| | 1 : 5 | 4 | 3 : 1 | 70* |
| (±)-**3** | 1 : 7 | 6,5 | 99 : 1 | 72 |

*Reduction carried out at 22°C.

indole **3** was used in racemic form. We had already established that the maximum diastereoselectivity in the reduction of indole (*S*)-**1** is observed using boron hydride complexes. The best result, giving about 80% diastereomeric excess, was obtained using sodium cyanoborohydride in methanol saturated with hydrogen chloride at −80°C [1]. These conditions were thus selected for the reduction of model indoles **1-3**.

The ratio of the diastereomers formed in the reduction of indoles **1-3** was found using PMR spectroscopy relative to the ratio of the integral intensities of the proton at $C_{(2)}$ of the indoline product. The PMR spectrum of a mixture of indolines (2*S*,1′*S*)-**4** and (2*R*,1′*S*)-**4** formed in the reduction of indole (*S*)-**1** shows a double set of virtually all the aliphatic proton signals. The 2-H signal for the major isomer (2*S*,1′*S*)-**4** is seen at 3.775 ppm, while the signal for this proton of the minor isomer (2*R*,1′*S*)-**4** is seen at 3.974 ppm ($\Delta\delta$ 0.2 ppm). The configuration of the new chiral site in indoline (2*S*,1′*S*)-**4** was found in our previous work [1]. For a preliminary determination of the configuration of the chiral site formed in the indolines obtained in the reduction of indoles **2** and **3**, we assumed that the relative position of the signals of the protons at the other unaltered chiral site remains constant in the case of diastereomers differing in the configuration of a single chiral site. The reduction conditions and ratio of the diastereomers obtained in the reduction of indoles **1-3** are given in Table 1.

The experimental data give rise to several important questions. Firstly, what is the reason for the predominant or even exclusive formation of the (2*S*,1′*S*)-diastereomer of the substituted indoline in the reduction of (*S*)-N-phenyl- and (*S*)-N-benzylethyl-2-R-indoles?

In order to answer this question, we must know the reaction mechanism and key features of the step in which the hydrogen atom of the reducing agent reacts with the indole $C_{(2)}$ atom, responsible for discrimination between two approaches of the reagent to the plane of the indole system. In principle, the ionic reduction of A=B multiple bonds [3] may proceed concertedly (with the simultaneous formation of A—H and B—H bonds) or stepwise. This may be represented clearly using a More O'Ferrall—Jencks diagram [4, 5] (Fig. 1), in which the formation of the A—H bond between the electron-rich atom of the double bond and the proton of the acid component of the reducing system is shown on the x-axis and the formation of the B—H bond between the electron-depleted atom of the double bond and a hydride ion from the reducing agent is shown along the y-axis. Curve *1* in this figure shows a stepwise mechanism, whose first step is protonation of the electron-rich end of the double bond. A stepwise mechanism with initial interaction of the hydride ion with the electron-depleted end of the double bond and subsequent protonation of the $^-$A—BH anion formed is described by curve *2*. The concerted mechanism with simultaneous formation of both bonds, perhaps with some asynchronicity, is shown by curve *3*.

The reaction mechanism depends on the relative stability of the anionic and cationic intermediates. If the proton transfer from HX to A=B is much more exothermic than transfer of a hydride ion from HM, the reaction proceeds stepwise through a cationic intermediate (curve *1* in Fig. 1). In the opposite case, the reaction proceeds through an anionic intermediate (curve *1* in Fig. 1). If, however, the heat effects of these two processes are similar, the reaction should proceed through a concerted mechanism (curve *3* in Fig. 1). In this case, the position of the transition state depends also on the relative energy of the cationic and anionic intermediates and the exothermicity of the reaction. According to the Hammond principle [6], the transition state becomes more reagent-like with increasing exothermicity of the reaction. Furthermore, the transition state has some carbocation nature if the energy of the intermediate state [HA — $B^+$ + $X^-$ + HM] is lower than the energy of the intermediate state [$^-$A — BH + HX + $M^+$] and some anionic character in the opposite case when the stabilities of these states are reversed. The reaction transition state is increasingly shifted toward the more stable state with increasing difference in energy between these two states (Thornton rule [7]). If this difference is sufficiently great, we find a shift in the reaction

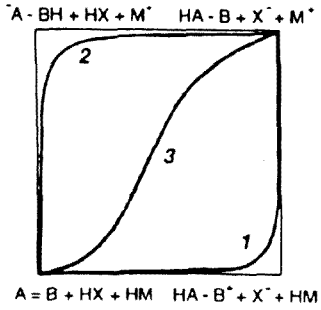
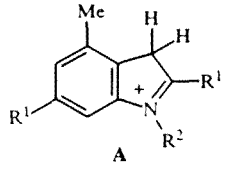
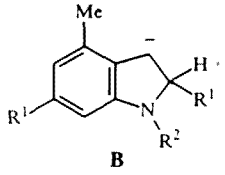



Fig. 1. More O'Ferrall—Jencks diagram for the ionic hydrogenation of the A=B bond.

mechanism from concerted to stepwise. For the ionic reduction of indoles **1-3**, these states are represented by structures **A** and **B**, respectively.




**A**




**B**

According to quantum chemical calculations, structure **A** is much more stable than structure **B**. This finding is in accord with the experimental data. Indole derivatives rapidly undergo electrophilic substitution, while aromatic nucleophilic substitution in the case of unactivated indoles cannot be carried out under ordinary conditions. Hence, we propose that the ionic reduction of indoles **1-3** may proceed stepwise through cationic intermediate **A**. This conclusion was supported by the finding of a stepwise mechanism for the ionic reduction of indole derivatives through a cationic intermediate using an isotope label technique and variation of the reaction conditions [8]. Thus, the stereodifferentiation upon the reduction of indoles containing a chiral substituent on the nitrogen atom occurs in the second step upon reaction of the indoleninium cation with $NaBH_3CN$ and is a function of 1,3-asymmetric induction.

The diastereoselectivity of this reaction may arise both from steric and thermodynamic factors. Thermodynamic control of the diastereoselectivity is indicated by the finding that the reaction of indoleninium cation **A** with $NaBH_3CN$ should be an exothermic reaction. The first protonation step featuring partial destruction of the indole aromatic system in the ionic reduction of indoles **1-3** is more likely rate-determining than the second step, in which optical activity is induced at $C_{(2)}$.

In the case of thermodynamic control of the diastereoselectivity of this reaction, the experimentally obtained diastereomer ratio is a function of the difference in the energies of the formation of the different diastereomers. In the case of kinetic control, this ratio in the absence of any specific interactions in the transition state should be intermediate between the corresponding values in the indoleninium cation (found to be 1:1) and in the indoline formed. In other words, the reduction diastereoselectivity in both cases should depend on the relative stability of the (2*S*,1′*S*) and (2*R*,1′*S*) diastereomers of the substituted indoline formed. Thus, we carried out AM1 quantum chemical calculations of all the possible conformers of model indolines **7-9**.

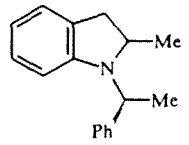
The substituent at the nitrogen atom in indolines **7-9** may be found either in the *syn* or *anti* position relative to the substituent at $C_{(2)}$ (Fig. 2).

We carried out calculations for all the possible conformations of the (2*S*,1′*S*) and (2*R*,1′*S*) diastereomers of N-α-phenylethyl-2-methylindoline **7** with *syn* and *anti* arrangement of these two substituents. The conformer with *anti* orientation of the substituents at $C_{(2)}$ and at the nitrogen atom in all cases were found to be much more stable than the *syn* analogs (Table 2). Similar data were obtained for indolines **8** and **9**. Thus, only the conformers of **7-9** with *anti* arrangement of the alkyl groups at $N_{(1)}$ and $C_{(2)}$ were considered.

Conformer *C* with the phenyl group of the N-phenylethyl substituent oriented almost perpendicularly to the plane of the indole system is the most stable of the three possible rotamers of (2*S*,1′*S*)-N-α-phenylethyl-2-methylindoline **7a** (Fig. 3). This orientation minimizes the steric repulsion between the bulkiest substituents, as seen in Fig. 4. Indeed, there is only one

TABLE 2. $H_{(20)}C_{(5)}N_{(1)}C_{(2)}$ Dihedral Angles and Heats of Formation of Various Conformers of N-α-Phenylethyl-2-methylindoline with *Syn* and *Anti* Arrangement of the Substituents at $N_{(1)}$ and $C_{(2)}$

| (2S,1'S) | | | | (2R,1'S) | | | |
|---|---|---|---|---|---|---|---|
| anti- | | syn- | | anti- | | syn- | |
| Θ | $\Delta E^f_{0,0}$ | Θ | $\Delta E^f_{0,0}$ | Θ | $\Delta E^f_{0,0}$ | Θ | $\Delta E^f_{0,0}$ |
| -49 | 55,0 | -37 | 57,4 | -17 | 56,8 | -25 | 58,3 |
| 63 | 57,7 | 68 | 59,1 | 51 | 55,9 | 47 | 56,9 |
| 167 | 55,9 | 177 | 57,2 | 179 | 55,5 | 168 | 56,8 |

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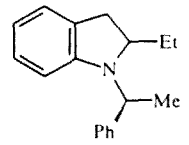


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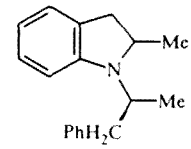


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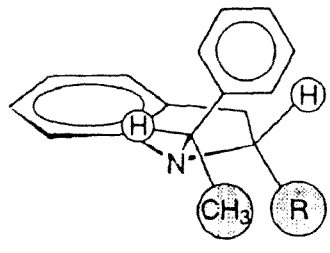
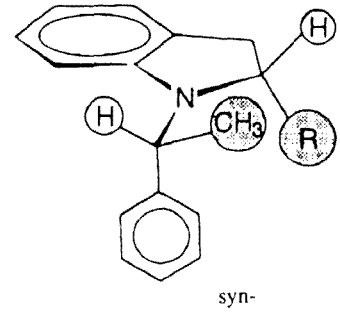



anti-




syn-

Fig. 2. Isomers of (2*S*,1'*S*)-N-α-phenylethyl-2-R-indoline with *anti* and *syn* orientation of the α-phenylethyl group relative to the substituent at $C_{(2)}$.

serious steric repulsion between two methyl groups in conformer **C**. There is also only one repulsion in conformer **D** but between the bulkier aryl fragments. On the other hand, conformer **E** has two undesirable steric interactions, which significantly raises its energy relative to **C** and **D**.

A similar situation is found for (2*R*,1'*S*)-N-α-phenylethyl-2-methylindoline **7b**. The rotamer with perpendicular orientation of the phenyl group of the substituent at nitrogen and the indoline system is also the most stable (Fig. 5).

However, an interaction of the methyl group of the phenylethyl substituent with the aryl fragment of the indole ring, which has higher steric strain energy, is observed in rotamer **F** instead of repulsion between two methyl groups. This results in higher energy of the most stable rotamer of (2*R*,1'*S*)-N-α-phenylethyl-2-methylindoline in comparison with the (2*S*,1'*S*) diastereomer. Using the data in Table 2, we calculated the equilibrium ratio of the (2*S*,1'*S*) and (2*R*,1'*S*) diastereomers of N-α-phenylethyl-2-methylindoline at various temperatures. This ratio is 73:27 at −80°C and is in good accord with the experimental finding of a significant preference for formation of the (2*S*,1'*S*) diastereomer. Thus the AM1 quantum chemical calculations show that the (2*S*,1'*S*) diastereomer of N-α-phenylethyl-2-methylindoline has greater stability than the (2*R*,1'*S*) isomer, which accounts for the predominant formation of the (2*S*,1'*S*) diastereomer in the ionic reduction of N-α-phenylethyl-2-methylindole.

Similar calculations were carried out for indolines **8** and **9**. Calculated energies of formation of the different conformers of these compounds are given in Table 3. Analysis of these data shows that the order of relative stability of the rotamers in these indolines is the same as in indoline **7**. The increase in the bulk of the alkyl group in the more stable conformer of the (2*S*,1'*S*) diastereomer of indoline **8** leads to a higher steric repulsion energy between the substituents (see rotamer **C**). This effect is lacking in the most stable conformer of the (2*R*,1'*S*) diastereomer of indoline **8**. As a result, the calculated

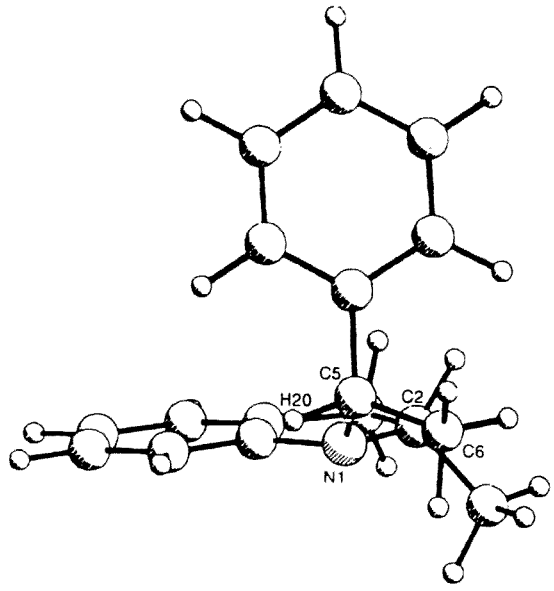
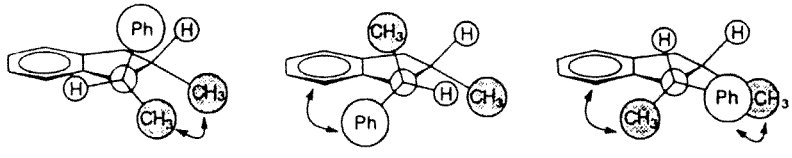
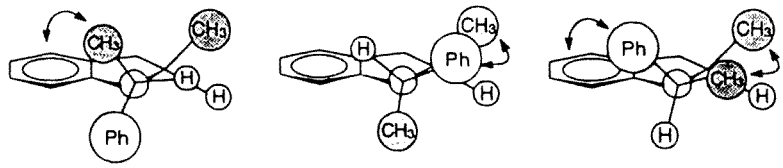



Fig. 3. Most stable rotamer of (2*S*,1′*S*)-N-α-phenylethyl-2-methylindoline **7a**.




C D E

Fig. 4. Rotamers of (2*S*,1′*S*)-N-α-phenylethyl-2-methylindoline **7a**.




F G H

Fig. 5. Rotamers of (2*R*,1′*S*)-N-α-phenylethyl-2-methylindoline **7b**.

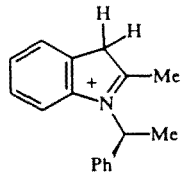
diastereomer equilibrium ratio (2*S*,1′*S*)/(2*R*,1′*S*) is somewhat lower (63:37) than for indoline **7**. Going from the N-α-phenylethyl substituent at the nitrogen atom to an α-benzylethyl group (indoline **9**) gives a marked decrease in the steric repulsion energy in those conformations, where the phenyl group of the benzyl fragment is most removed from the indoline fragment. This permits a twist of the substituent at the nitrogen atom about the C—N bond, decreasing the repulsion between the two methyl groups (conformer **C** for the (2*S*,1′*S*) diastereomer) or methyl and aryl group (conformer **F** for the (2*R*,1′*S*) diastereomer). Comparison of the $H_{(20)}C_{(5)}N_{(1)}C_{(2)}$ dihedral angles in Tables 2 and 3 shows the importance of this twist. A somewhat greater substituent effect is observed for the (2*R*,1′*S*) diastereomer, which, as in the case of indoline **8**, leads to a reduction calculated (2*S*,1′*S*)/(2*R*,1′*S*) diastereomer equilibrium ratio (64:36). Nevertheless, the quantum chemical calculations for all indolines **7-9** shows greater thermodynamic stability for the (2*S*,1′*S*) diastereomer in comparison with the

TABLE 3. $H_{(20)}C_{(5)}N_{(1)}C_{(2)}$ Dihedral Angles and Heats of Formation of Various Rotamers at the $N_{(1)}—C_{(2)}$ Bond of the (2*S*,1′*S*) and (2*R*,1′*S*) Diastereomers of Indolines **8** and **9**

| Indoline | (2*S*,1′*S*) | | (2*R*,1′*S*) | |
|---|---|---|---|---|
| | $\Theta_{H(20)C(5)N(1)C(2)}$ | $\Delta E^f_{0,0}$ | $\Theta_{H(20)C(5)N(1)C(2)}$ | $\Delta E^f_{0,0}$ |
| 8 | -49 | 48,9 | -52 | 51,2 |
| | 68 | 51,7 | 58 | 49,7 |
| | 169 | 49,7 | 178 | 49,3 |
| 9 | -55 | 47,1 | -46 | 48,7 |
| | 43 | 49,4 | 54 | 47,4 |
| | 159 | 48,3 | 167 | 48,6 |

(2*R*,1′*S*) isomer, which suggests a significant effect of the thermodynamic factor on the diastereoselectivity of the ionic reduction of substituted indoles such as **1-3**.

On the other hand, the (2*S*,1′*S*)/(2*R*,1′*S*) diastereomer ratio in all cases proved much lower than the experimentally determined diastereoselectivity for the reduction of indoles **1-3** to give the corresponding indolines **4-6**. This may be attributed to specific interactions in the transition state absent in the indolines upon kinetic control of the diastereoselectivity of reduction. The experimental data on the temperature effect of the reduction diastereoselectivity of indole **2** may serve as evidence for this hypothesis. Indeed, the reduction diastereoselectivity at 22°C was only 3:1, which corresponds to a difference in the activation energies for the two approaches of the boron hydride reagent to the plane of the indole system of 0.4 kcal/mole, and similar to the values obtained in calculations for the relative stability of the diastereomers of the indoline formed. However, complete diastereoselectivity (>99:1) is found for the reduction at −80°C, which corresponds to a difference in activation energy of the two competing processes of more than 2 kcal/mole. Such results are usually obtained if rotation of the chiral substituent is free at one temperature and hindered, even though partially, at a lower temperature. In the former case, the system conforms to the Curtin—Hammett principle [9], while a deviation from this principle is observed in the latter. Then, the diastereoselectivity at 22°C is a function of the relative energies of the transition states leading to the (2*S*,1′*S*) and (2*R*,1′*S*) diastereomers, respectively. At −80°C, the diastereoselectivity is a function of the relative energies of the pro-*S* and pro-*R* conformations of the intermediate indoleninium cations. In order to check this hypothesis, we calculated various conformations of indoleninium cations **10-12** and the potential energy surface for rotation of the chiral substituent at the nitrogen atom about the C—N bond in cations **10-12** and in resultant indolines **7-9**.



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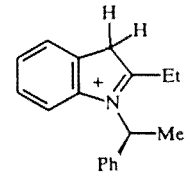
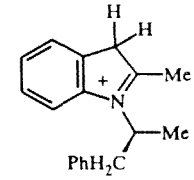


**11**



**12**

The potential energy surfaces of indoline **7** and cation **11** are given as examples in Figs. 6 and 7.

These data indicate that the rotational barrier of the chiral substituent at the nitrogen atom at room temperature (3.3-4.2 kcal/mole) is quite small, permitting free rotation of this substituent and, thus, interaction of the boron hydride reagent with all the conformations of the indoleninium cation. As a result, the diastereoselectivity of the reaction at room temperature is a function of the relative energies of all the possible conformations of the transition state leading both to the (2*S*,1′*S*) and (2*R*,1′*S*) indoline diastereomers. However, at −80°C, this rotation is rather hindered, such that the diastereoselectivity of the reduction is a function of the relative stability of the pro-*S* and pro-*R* conformations of the indoleninium cation and not of the corresponding transition state energies. At −80°C, the calculated ratio of these conformations is 95:5 for cation **10**, 88:12 for **11**, and 91:9 for **12**, which is attributed to the greater interaction energy of the counter-ion with the phenyl group of the substituent at the nitrogen atom than with the methyl group (Fig. 8).

Thus, the reduction diastereoselectivity is a function of the energies of the corresponding transition states at 22°C and of the relative energies of the pro-*S* and pro-*R* conformations of the intermediate indoleninium cation. The calculated ratio of these conformations is in rather good accord with the experimental data. The effects of other substituents, the solvent, and other factors are presently under study.

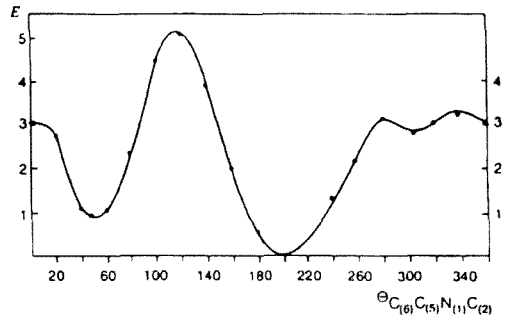



Fig. 6. Potential energy surface for the α-phenylethyl substituent about the C—N bond in indoline **7**.

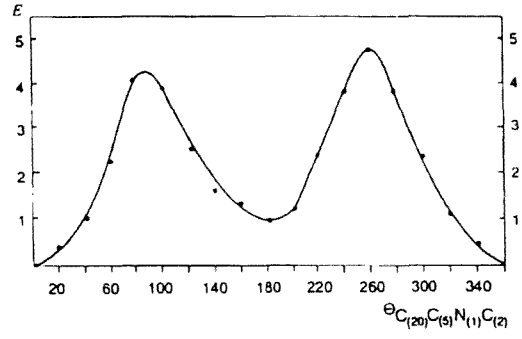



Fig. 7. Potential energy surface for the α-phenylethyl substituent about the C—N bond in indoleninium cation **11**.

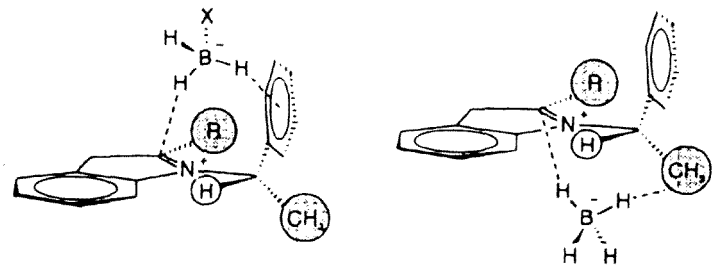
## EXPERIMENTAL

The PMR spectra were taken on a Varian VXR-400 spectrometer for solutions in $CDCl_3$ relative to TMS as the internal standard. The specific rotation was measured on a Jasco DIP-360 polarimeter. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol plates using 1:9 benzene—hexane as the eluent.

The samples of (*S*)-α-phenylethylamine had 96.5% optical purity, $[\alpha]_D$ −39° (without solvent). The procedure for the preparation of the acetonimine of (*S*)-α-phenylethylamine has been described in our previous work [1] and the acetonimine of (±)-α-benzylethylamine was similarly obtained. In order to avoid hydrolysis and other transformations, the unstable acetonimines were used in reactions with the 3-nitropyridine salts without any purification.

**The AM1 semiempirical quantum chemical calculations** were carried out using the MOPAC 7.0 program package for personal computers. Since semiempirical calculations often lead to several configurational minima for one molecular conformation, the global minimum for each conformation was determined using at least three calculations with different starting geometries. All the calculations were carried out using the key word PRECISE. Calculation of the potential energy surface of the system upon rotation of the substituent at the nitrogen atom about the C—N bond was performed by varying the corresponding dihedral angle, using optimized geometries of each conformation and selecting the most stable molecular configurations obtained at a given dihedral angle.

**(*S*)-1-(1-Methylbenzyl)-2,4,6-trimethylindole (1).** A solution of isopropylidene(1-methylbenzyl)amine obtained from 0.725 g (6 mmoles) (*S*)-α-phenylethylamine in 5 ml DMF was added in portions to a solution of 0.924 g (3 mmoles) 1,2,4,6-tetramethyl-3-nitropyridinium iodide and 2.81 g (18 mmoles) (*S*)-α-phenylethylamine hydrochloride in 15 ml DMF. The reaction mixture was maintained for 48 h and the solvent was evaporated to one-third original volume. The residue was diluted with 100 ml water and extracted with three 50-ml portions of hexane. The extract was washed with 10% hydrochloric acid, several times with water, and saturated aqueous sodium chloride. After evaporation of the solvent, the residue was subjected to chromatography on a silica gel column using 3:7 benzene—hexane as the eluent to give 0.6 g (75%) indole **7** as



pro-S pro-R

Fig. 8. Pro-*S* and pro-*R* conformations of the boron hydride ion pair with the most stable rotamer of the (*S*)-N-α-phenylethyl-2-R-indoleninium cation.

a light yellow oil. PMR spectrum: 1.92 (3H, d, $J$ = 7 Hz, $CHC\underline{H}_3$), 2.31 (3H, s, 2-$CH_3$), 2.47 (3H, s, 6-$CH_3$), 5.72 (1H, q, $J$ = 7 Hz, $C\underline{H}CH_3$), 6.24 (1h, br.s, 3-H), 6.67 (1H, br.s, 5-H), 6.70 (1H, br.s, 7-H), 7.13-7.35 ppm (5H, Ph). Found: C, 86.65; H, 8.01%; N, 5.34%. Calculated for $C_{19}H_{21}N$: C, 86.70; N, 7.98; N, 5.32%. $[\alpha]_D^{25}$ +8.4° (c 0.81, hexane).

α-Phenylethylamine was isolated from the aqueous phase after the extraction.

Analogous procedures yielded:

**(*S*)-1-(1-Methylbenzyl)-2,6-diethyl-4-methylindole (2)** was obtained in 70% yield as a light yellow oil. PMR spectrum: 1.27 (3H, t, $J$ = 7.4 Hz, $C\underline{H}_3CH_2$), 1.45 (3H, t, $J$ = 7.5 Hz, $C\underline{H}_3CH_2$), 2.04 (3H, d, $CHC\underline{H}_3$), 2.62 (3H, s, 4-$CH_3$), 2.70 (2H, q, $C\underline{H}_2CH_3$), 2.85 (2H, q, $C\underline{H}_2CH_3$), 5.84 (1H, q, $J$ = 7.1 Hz, $C\underline{H}CH_3$), 6.41 (1H, br.s, 3-H), 6.77 (1H, br.s, 5-H), 6.83 (1h, br.s, 7-H), 7.26-7.45 ppm (5H, m, $C_6H_5$). Found: C, 86.66; H, 8.64; N, 7.40%. Calculated for $C_{21}H_{25}N$: C, 86.59; H, 8.59; N, 4.82%. $[\alpha]_D^{25}$ −3.2° (s 5.86, benzene).

**(±)-1-(1-Ethylbenzyl)-2,4,6-trimethylindole (3)** was obtained in 65% yield as a light yellow oil. PMR spectrum in $CDCl_3$: 1.34 (3H, m, $C\underline{H}_3CH$), 2.12 (3H, s, 2-$CH_3$), 2.60 (3H, s, 4-$CH_3$), 2.64 (2H, s, 6-$CH_3$), 3.18 and 3.42 (2H, 2m, $C\underline{H}_2C_6H_5$), 4.41 (1H, m, $C\underline{H}N$), 6.32 (1H, br.s, 3-H), 6.98-7.42 ppm (7H, m, $H_{Ar}$). Found: C, 86.71; H, 8.39; N, 4.90%. Calculated for $C_{20}H_{23}N$: C, 86.64; H, 8.31; N, 5.05%.

**Reduction of Indoles to Indolines (general procedure).** A solution of 0.2 mole indole in 5 ml methanol saturated with hydrogen chloride was cooled to −90°C and sodium cyanoborohydride was added in portions with vigorous stirring maintaining the temperature at from −85 to −75°C. The reaction mixture was stirred for 1.5-2 h at the same temperature, neutralized by adding 2 N NaOH, and extracted with benzene. The benzene extracts were dried over $Na_2SO_4$. The solvent was evaporated at reduced pressure. The residue was subjected to chromatography on a silica gel column using 1:4 benzene—hexane as the eluent to give a mixture of diastereomeric indoles. The ratio of the diastereomers was determined using NMR and high-efficiency liquid chromatography.

The authors express their gratitude to the Russian Basic Research Fund for financial supports of their studies (Grant No. 96-03-32157).

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